Review Article

Role of immune system modulation in prevention of type 1 diabetes mellitus

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ABSTRACT

An increased incidence of Type 1 diabetes mellitus (T1DM) is expected worldwide. Eventually, T1DM is fatal unless treated with insulin. The expansion of interventions to prevent diabetes and the use of alternative treatments to insulin is a dream to be fulfilled. The pathophysiology in T1DM is basically a destruction of beta cells in the pancreas, regardless of which risk factors or causative entities have been present. Individual risk factors can have separate patho-physiological processes to, in turn, cause this beta cell destruction. Currently, autoimmunity is considered the major factor in the pathophysiology of T1DM. In a genetically susceptible individual, viral infection may stimulate the production of antibodies against a viral protein that trigger an autoimmune response against antigenically similar beta cell molecules. Many components of the immune system have been implicated in autoimmunity leading to β-cell destruction, including cytotoxic and helper T-cells, B-cells, macrophages, and dendritic cells. The inflammatory process in early diabetes is thought to be initiated and propagated by the effect of Th1-secreted cytokines (e.g. g interferon) and suppressed by Th2-secreted antiinflammatory cytokines (interleukins). Structure and function of β-cell may be modulated by using Th1/Th2-secreted cytokines. Several experimental and clinical trials of applying GAD65, Hsp60, peptide-MHC, pepetide-277 immunization, anti-CD3 infusion, and interleukins to modulate immune response in T1DM were done. Applying such trials in patients with prediabetes, will most likely be the future key in preventing Type 1 autoimmune diabetes.

Key words: Immune modulation, prevention, type 1 diabetes

Introduction

Type 1 diabetes mellitus (T1DM) is characterized by T cell-mediated selective destruction of insulin-producing β-cells. Despite modern medical management, T1DM is still associated with a mortality rate three to four times higher than that of the background population. Exogenous insulin has been the core of treatment for T1DM since its discovery in 1921. While this enables most diabetics to live a near normal life, it is not without complications that may imperil the life of patients.[1-3]

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The expansion of interventions to prevent diabetes and the use of alternative treatments to insulin is a dream to be fulfilled. Cyclosporin trials in the 1980s reported temporary remission in newly diagnosed T1DM proving the principle that manipulation of the immune system may alter the course of the disease.[4] Although the knowledge of the pathophysiology and nature of the disease has grown, the capability to interfere effectively to prevent, reverse, or even delay the clinical onset of disease is unchanged. New strategies for early intervention and disease prevention are required. The development of such interventions depends mainly on the understanding details of the nature of T1DM.

Pathophysiology

Inside the pancreas in normal persons, there are about million islets of Langerhans. Four major cell types are present in the islets. Beta (β) cells which secret insulin and are located centrally within the islets, Alpha (α) cells which

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secrete glucagon, Delta (δ) cells which secrete somatostatin, and PP cells which secrete pancreatic polypeptide.[5] Insulin is a peptide hormone composed of 51 amino acids. At first it is synthesized as preproinsulin in the ribosomes of the rough endoplasmic reticulum. The preproinsulin is then cleaved into proinsulin that moves to the Golgi apparatus where it is packaged into secretory granules. In the secretory granules proinsulin is cleaved into equimolar amounts of insulin and a residual connecting peptide, or C-peptide. In T1DM, beta cell mass decreases as a sequelae of autoimmune process. Fasting blood glucose level raises, followed by inability to keep postprandial below 200 mg/dL. Transient insulin resistance is also seen in untreated T1DM. Initially, there is excessive secretion of glucagon relative to insulin after protein meals. By way of time, there is continued loss of islets, with glucagon deficiency, making patients more susceptible to insulin- induced hypoglycemia.[6-9]

The stage of prediabetes

Several years of progressive autoimmune β-cell damage usually precede the clinical onset of diabetes. Although careful testing reveals loss of the first phase of insulin release, this long prediabetes phase is asymptomatic. When the β-cell mass has been eroded to a critical level, falling insulin secretion can no longer restrain hyperglycemia and clinical diabetes develops. Some newly diagnosed T1DM are C-peptide positive, and β-cell secretion may improve temporarily when insulin treatment is started. With continuing β-cell destruction, endogenous insulin production declines progressively and more than 90% of T1DM become permanently C-peptide negative within 5 years of presentation. The loss of C-peptide is more rapid in individuals diagnosed in childhood than in new onset disease in adults. Eventually, insulitis burns itself out and the immune cells retreat, leaving islet remnants that are devoid of β cells but still contain intact α, δ, and PP cells.[10,11] The prolonged prediabetic phase provides an opportunity to prevent individuals with active insulitis from developing clinical disease.

Genetic factors in Type 1 diabetes mellitus

Previous studies established that, the susceptibility to T1DM—not the disease itself—is inherited. Certain genetic alterations increase or decrease the risk of β-cell damage. The most significant genetic linkage to T1DM is the human leukocyte antigen (HLA) group, the family of genes that controls antigen presentation within the immune system. Inheritance of HLA antigens DR3 and DR4 is associated with an increased risk of developing T1DM. Antigen presentation is a critical aspect of T-lymphocyte activation.[12] Gabbay *et al*. noted that, HLA-DR3, DR4 or DR3/DR4 and PTPN22 polymorphism did not show any association with pancreatic islet cell antibodies or studied cytokines.[13] However, a combination of autoantibody titres and genetic markers (HLA haplotypes) can be used to predict the chances of the disease developing in high risk individuals such as the siblings of children with T1DM.

Auto-antigens in Type 1 diabetes mellitus

About 80% of patients with new onset T1DM have islet cell antibodies. There are a variety of antibodies against β cell constituents including glutamic acid decarboxylase (GAD) (GAD 65 and GAD 67), and the secretory granule protein islet cell antigen (ICA) 512 or IA-2. These antibody positive individuals—within many years—are at risk of developing T1DM. The probability of developing T1DM is greater than 50% if autoantibodies are present to more than one β-cell antigen (i.e. γ insulin, GAD 65, ICA 512). However, these antibodies appear to be markers for, rather than the cause of, β-cell injury. Destruction of β-cell is mediated by a variety of cytokines or by direct T/B-lymphocyte activity.[14-16]

Role of Immune Process

During the initial phase of autoimmune destructive process, some viable β-cells are still present producing enough insulin. By time, nearly all b-cells are destroyed and the patient becomes totally exogenous insulin dependent. The damage to β-cells might be initiated by direct viral, environmental toxins, and/or a primary immune attack against specific β-cell antigens such as GAD65. T-helper lymphocytes (CD4+) are activated by β-cell antigens and antigen-presenting cells (macrophage or dendritic cells). Macrophages secrete interleukin (IL)-12, stimulating CD4 + T cells to secrete interferon (IFN)-γ and IL-2. IFN-γ stimulates other resting macrophages to release in turn, other cytokines such as IL-1β, tumor necrosis factor (TNF-α) and free radicals, which are toxic to β-cells. Further, activated T-helper cells produce cytokines that attract T and B lymphocytes and encourage them to proliferate in the islet leading to insulitis. B lymphocytes might then damage β-cells by producing antibodies against released β-cell antigens, while cytotoxic (CD8+) T lymphocytes directly attack β-cells carrying the target auto-antigens. Unpredictable process—such as environmental viral infections triggers—might flare up insulitis. The process may fade and abort for unknown reasons.[17-19]

Markers for prediction of Type 1 diabetes mellitus

Identifying individuals at risk before substantial islet injury is a challenge for diabetes prevention. If diabetes can be predicted earlier, it may be possible to prevent disease progression while an adequate islet mass remains to maintain euglycemia throughout the patient's lifetime. Several data

revealed that, individuals must lose 50–90% of their islet mass before onset of hyperglycemia.[20] At hand, the most highly predictive model for identifying people—not yet manifesting diabetes—depends on recognition of abnormal insulin secretion, and glucose intolerance. However, identification at this stage is relatively late where substantial islet injury occurs before finding this.[19] Consequently, all need predictive markers that measure abnormalities more remote from diabetes diagnosis. Detection of β-cell-directed autoantibodies in the blood is the target at present. Common markers include antibodies against the insulin molecule, GAD, zinc- transporter-8, and insulinoma antigen 2 (IA2). Antibodies against whole islets and insulin are specific to pancreatic β-cells, whereas, IA2 and GAD are nonspecific.[21,22] In addition, the histochemical islet cell antibody test (ICA) detects any immunoglobulin directed at intact human islets but does not identify the specific antigen(s). Several studies documented that, higher titers of ICA correspond to a higher 5- to 10-year risk of developing T1DM.[23,24] Alternatively, in established cases of T1DM, the residual β-cell function at diagnosis of T1DM could be assessed by measuring C-peptide secretion.

Immunomodulatory Intervention

On the base of the natural history of the disease process data, avoiding environmental triggers that would prevent the initiation of the autoimmune process may delay the progression of the disease. The likely benefits of intervention at these time points would depend on the nature of the intervention and the degree to which the autoimmune process could be halted or reversed. At the time of diagnosis, 5–20% of β-cells are still functioning and could be preserved. Therefore, early intervention with minimal side effects, before appearance of autoantibodies to β-cells is the ideal therapy especially in individuals at highest genetic risk. Nowadays, several goals are achieved including deactivation of islet-reactive lymphocytes, correction of the inflammatory milieu that injures islets and promotes lymphocyte activation, and restoration of an adequate islet mass.[25-27]

Antigen-specific and nonspecific interventions

To prevent the progression of T1DM, it is highly desirable to either correct the abnormal function or eliminate those lymphocytes that have targeted the β-cells. Initial trials for preventing the progression of early diabetes used immunosuppressive agents, including prednisone,[28] cyclosporine,[4] azathioprine,[29] and antithymocyte globulin.[30] These agents would suppress the islet cell inflammatory process induced by pathogenic T cells. However, the trials resulted only in a modest delay of diabetes in a minority of patients. No long-term effect was seen and discontinuation of the drugs caused the autoimmune process to recur. In addition, these agents are not safe enough for having variable degrees of toxicity.

Globally, it is well established that insulin itself is a primary target of the immune response, and modulation of antiinsulin reactivity may be beneficial. The oral insulin is metabolically inactive because of its degradation in the stomach as well. These degraded peptide products were hypothesized to possess immune-regulating potential. Depending on these hypotheses, two studies were designed to determine whether exposure to insulin, in ways thought to induce tolerance (oral administration or very-low-dose injection), could delay or prevent the onset of T1DM. In the first study, relatives predictable to have a 5-year risk of >50% for progression to T1DM were given low-dose parenteral insulin. In the second study, relatives with a <50% risk were given oral insulin. Unfortunately, neither intervention groups showed a significant delay in T1DM progression compared to placebo.[31] However, in animal model studies, both parenteral and oral insulin delayed or prevented disease onset, by acting either metabolically via allowing the β-cells to rest or immunologically via inducing tolerance or reducing T-cell infiltration into the pancreatic islets.[32,33]

Up till now, the full range of β-cell auto-antigens is still obscure. Many components of the immune system have been implicated in autoimmunity leading to T1DM, including cytotoxic and helper T-cells, B-cells, macrophages, and dendritic cells.[21] Since T-cells are the known end-stage effectors of islet destruction, nonspecific interventions directed against the T-lymphocyte have been widely used. According to Moore *et al.*, T-cells express CD3 along with CD4 or CD8 could in theory modulate T-cell response and therefore alter autoimmunity.[34] Targeting of the CD3 receptor with monoclonal antibodies has been tested on newly diagnosed patients with T1DM and showed improved insulin production 2 years after diagnosis but did not successfully lead to remission of the disease.[35]

Beside T-lymphocytes, B-lymphocytes also play a central role and are linked to the immunopathogenesis of T1DM. Depleting B-lymphocytes may prevent and reverse diabetes in mouse models.[36,37] Rituximab, an anti- CD20 chimeric antibody that depletes B-lymphocytes, has shown encouraging initial clinical results. A recent Trial- Net- funded study demonstrated that a four-dose course of rituximab could preserve β-cell function over a 1-year period in patients with newly diagnosed T1DM.[38] In addition, systemic antiinflammatory agents such as IL-1 receptor antagonists[39] and agents that stimulate β-cell proliferation[40] are being studied as potential components of a multidrug prevention of β-cell destruction.

Activation of natural killer cells (NKT) by a-galactosylceramide, inducing secretion of Th2 cytokines, has also been found to protect nonobese diabetic (NOD) mice from diabetes and prolong their survival.[41] Another approach that can skew the cytokine cascade from a Th1 to a Th2 response is the use of a nondepleting anti- CD3 antibody. Anti-CD3 monoclonal antibodies usually suppress immune responses by transient T-cell depletion and antigenic modulation of the CD3–T-cell receptor complex. On the basis of these observations, a randomized controlled trial in patients with new-onset T1DM was initiated. Twelve patients received a 14 day course of anti- CD3 monoclonal antibody hOKT31 intravenously. After 1 year, nine patients in the treatment group maintained or improved insulin production (as opposed to only 2 of the 12 controls) without strict side effects.[42]

GAD is a 65 kD protein that is found normally in islet cells. Antibodies to GAD appear early after the initiation of autoimmune insulitis. Injection of GAD65,[43,44] GAD 67 (isoform),[45] GAD-derived peptides,[46] a DNA plasmid expressing GAD,[47] anti-GAD monoclonal antibody,[48] GAD antisense DNA,[49] or a vaccinia virus expressing GAD[50] reduced the severity of insulitis and prevented the onset of diabetes in NOD mice.[51] Other antigen-specific interventions currently in development include the use of a GAD vaccine and the isolation and expansion of regulatory T-cells that are able to suppress islet-reactive lymphocytes in an antigen-specific manner.[52]

Seeing that the inflammatory process in early diabetes is thought to be initiated and propagated by the effect of Th1- secreted cytokines (e.g. γ interferon) and suppressed by Th2-secreted antiinflammatory cytokines (interleukins), diabetes can be prevented using Th2-secreted interleukins.[51] IL- 35 is a newly identified inhibitory cytokine used by T regulatory cells to control T cell-driven immune responses. Bettini *et al*. examined the therapeutic potential of native, biologically active IL-35. Expression of the hetero-dimeric IL-35 cytokine was targeted to β-cells via the rat insulin promoter II. Autoimmune diabetes, insulitis, and the infiltrating cellular populations were analyzed. Ectopic expression of IL-35 by pancreatic β-cells led to substantial, long-term protection against autoimmune diabetes, despite limited intra-islet IL-35 secretion. Although there were limited alterations in cytokine expression, the observed reduced CD4(+) and CD8(+) T-cell numbers coincided with diminished T-cell proliferation, hallmarks of IL-35 biological activity. Depending on this biological activity, IL-35 could be used as a potent inhibitor of autoimmune reactions and implicate its potential therapeutic utility in the treatment of T1DM.[53] Alternatively, IL-12 is a pivotal Th1-associated cytokine and a potent immunoregulatory molecule. Zhang *et al*. investigated whether intermittent administration of IL-12 could prevent the development of T1DM in NOD mice. Furthermore, they investigated the potential mechanisms of IL-12-mediated prevention of diabetes and insulitis. Their data had revealed that, IL-12 suppressed insulitis and increased the number of healthy islets, and the levels of IL-17, IL-1β, IL-6, and IL- 23 were significantly decreased. Moreover, IL-12 induced the secretion of IFN-γ, a potent inhibitor of Th17 cells. These results indicated that, intermittent administration of IL-12 prevented diabetes by inducing IFN-γ, suppressing the pathogenic IL-17-producing cells, and reducing the expression of Th17-associated pro-inflammatory cytokines.[54] Moreover, diabetes was persistently prevented by transfection of IL-4,[55] IL-10,[56] and IL-11[57] on several experimental trials. On the assumption that, interleukins had been successfully used in preventing chronic inflammatory process in animal models, their future use for intervention in individuals at risk for T1DM should be considered.

Another described approach for T-cell tolerance induction in diabetes is the use of tolerizing peptide-MHC dimers in which the peptide component is a peptide specific to the pathogenic T-cell clones. According to Masteller *et al*., *in vivo* treatment with such dimers protected mice from diabetes.[58]

Heat shock protein (Hsp) is a different important self antigen in the pathogenesis of diabetes. Antibodies directed against Hsp65 were found in NOD mice that were developing insulitis. These autoantibodies were not present in NOD mice that did not develop diabetes. Anti- Hsp60 T cell clones transplanted into healthy mice induced insulitis.[59]

The Hsp60 epitope recognized by T cells was identified as a 24 amino acid peptide termed peptide 277 (p277). Injection of p277 in mice exposed to low dose streptozotocin prevented both insulitis and diabetes.[60] Increased T-cell response to Hsp60 and p277 was observed in T1DM patients, suggesting a similar role of these proteins in human diabetes.[61] Based on the protective and therapeutic effects of p277 in animal models as well as the findings in the human disease, a human p277 vaccine has been developed. The efficacy of this vaccine was tested in a double-blind study in patients with recently diagnosed T1DM. The vaccine intervention group required significantly less exogenous insulin to achieve the same level of HbA1c (7%) at the end of the trial.[62]

Recent discussions have focused on combining an immunomodulator successful in preventing/reversing T1DM in preclinical studies and human trials with auto- antigen(s) and/or biologic agents that on their own improve the function and/or the mass of residual beta cells. These discussions have also proposed combining two or more immuno-modulators.

Examples include combining the anti-CD3 antibody with beta-cell-protective and function-enhancing GLP-1 agonist], IL-1-neutralising antibodies with the anti-CD3 antibody, and anti-CD3 antibodies with traditional pharmacologic immunosuppressives like rapamycin.[63] There is a realistic hope that GAD vaccination, perhaps in combination with vaccinations with other auto-antigens and/or other therapies, will result in remission for some patients. The prospects of cure and prevention of T1DM will become less remote.[64]

Conclusion

The current review outlined the advancement that has been made in different trials—to prevent, reverse, or even delay the sequences of T1DM—by modifying the immune assault on the β-cell. Successful experimental trials have been conducted to preserve insulin secretion. In contrast, clinical prevention studies have so far failed to produce satisfactory and safe positive results. However, such trials are feasible and have identified new promising agents for future T1DM prevention strategy.

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References

1. Atkinson MA, Eisenbarth GS. Type 1 diabetes: New perspectives on disease pathogenesis and treatment. Lancet 2001;358:221-9.
2. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltész G. Incidence trends for type 1 diabetes in Europe during 1998-2003 and predicted new cases 2005020: A multicentre prospective registration study. Lancet 2009;373:2027-33.
3. Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burden AC, Waugh NR, *et al.* The British diabeteic association cohort study, II: Cause-specific mortality in patients with insulin –treated diabetes mellitus. Diabet Med 1999;16:466-71
4. Bougneres PF, Landais P, Boison C, Carel JC, Frament N, Boitard C, *et al*. Limited duration of remission of insulin dependency in children with recent overt type 1 diabetes treated with low- dose cyclosporin. Diabetes 1990;39:1264-72.
5. Shapiro AM, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, *et al*. International trial of the Edmonton protocol for islet transplantation. N Engl J Med 2006;355:1318-30.
6. Pilkis SJ, Granner DK. Molecular physiology of the regulation of hepatic gluconeogenesis and glycolysis. Annu Rev Physiol 1992;54:885-909.
7. Gerich JE, Lorenzi M, Bier DM, Schneider V, Tsalikian E, Karam JH, *et al.* Prevention of human diabetic ketoacidosis by somatostatin. Evidence for an essential role of glucagon. N Engl J Med 1975;292:985-9.
8. Gerich JE, Langlois M, Noacco C, Karam JH, Forsham PH. Lack of glucagon response to hypoglycemia in diabetes: Evidence for an intrinsic pancreatic alpha cell defect. Science 1973;182:171-3.
9. Raskin P, Unger RH. Hyperglucagonemia and its suppression. Importance in the metabolic control of diabetes. N Engl J Med 1978;299:433-6.
10. Exton JH. Mechanisms of hormonal regulation of hepatic glucose metabolism. Diabetes Metab Rev 1987;3:163-83.
11. Haller MJ, Atkinson MA, Schatz D. Type 1 diabetes mellitus: Etiology, presentation, and management. Pediatr Clin North Am 2005;52:1553-78.
12. Steck AK, Zhang W, Bugawan TL, Barriga KJ, Blair A, Erlich HA, *et al*. Do non-HLA genes influence development of persistent islet autoimmunity and type 1 diabetes in children with high-risk HLA- DR,DQ genotypes? Diabetes 2009;58:1028-33.
13. Gabbay MA, Sato MN, Duarte AJ, Dib SA. Serum titres of anti- glutamic acid decarboxylase-65 and anti-IA-2 autoantibodies are associated with different immunoregulatory milieu in newly diagnosed type 1 diabetes patients. Clin Exp Immunol 2012;168:60- 7.
14. Harrison LC, Honeyman MC, De Aizpurua HJ, Schmidli RS, Colman PG, Tait BD, *et al*. Inverse relation between humoral and cellular immunity to glutamic acid decarboxylase in subjects at risk of insulin-dependent diabetes. Lancet 1993;341:1365-9.
15. Kaufman DL, Clare-Salzler M, Tian J, Forsthuber T, Ting GS, Robinson P, *et al*. Spontaneous loss of T-cell tolerance to glutamic acid decarboxylase in murine insulin-dependent diabetes. Nature 1993;366:69-72.
16. Orban T, Sosenko JM, Cuthbertson D, Krischer JP, Skyler JS, Jackson R, *et al*. Pancreatic islet autoantibodies as predictors of type 1 diabetes in the Diabetes Prevention Trial-Type 1 (DPT-1). Diabetes Care 2009;32:2269-74.
17. Gelber C, Paborsky L, Singer S, McAteer D, Tisch R, Jolicoeur C, *et al.* Isolation of nonobese diabetic mouse T-cells that recognize novel autoantigens involved in the early events of diabetes. Diabetes 1994;43:33-9.
18. Maclaren N, Lan M, Coutant R, Schatz D, Silverstein J, Muir A, *et al.* Only multiple autoantibodies to islet cells (ICA), insulin, GAD65, IA-2 and IA-2beta predict immune-mediated (Type 1) diabetes in relatives. J Autoimmun 1999;12:279-87.
19. Sabbah E, Savola K, Kulmala P, Veijola R, Vähäsalo P, Karjalainen J, *et al*. Diabetes-associated autoantibodies in relation to clinical characteristics and natural course in children with newly diagnosed type 1 diabetes. J Clin Endocrinol Metab 1999;84:1534-9.
20. Mahon JL, Sosenko JM, Rafkin-Mervis L. The TrialNet natural history study of the development of type 1 diabetes: Objectives, design, and initial results. Pediatr Diabetes 2009;10:97-104.
21. Atkinson MA, Bowman MA, Campbell L, Darrow BL, Kaufman DL, Maclaren N.K. Cellular immunity to a determinant common to glutamate decarboxylase and coxsackie virus in insulin-dependent diabetes. J Clin Invest 1994;94:2125-9.
22. Ellis TM, Schatz DA, Ottendorfer EW, Lan MS, Wasserfall C, Salisbury PJ, *et al.* The relationship between humoral and cellular immunity to IA-2 in IDDM. Diabetes 1998;47:566-9.
23. Verge CF, Gianani R, Kawasaki E, Yu L, Pietropaolo M, Jackson RA, *et al*. Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/ IA-2 autoantibodies. Diabetes 1996;45:926-33.
24. Barker JM, Barriga KJ, Yu L, Miao D, Erlich HA, Norris JM, Eisenbarth GS Rewers M. Prediction of auto-antibody positivity and progression to type 1 diabetes: Diabetes Auto-immunity Study in the Young. J Clin Endocrinol Metab 2004;89(8):3896-902.
25. Thrower SL, Bingley PJ. Prevention of type 1 diabetes. Br Med Bull 2011;99:73-88.
26. Alhadj Ali M, Dayan CM. The importance of residual endogenous beta-cell preservation in type 1 diabetes. Br J Diabetes Vasc Dis 2009;9:248-53.
27. von Herrath M, Sanda S, Herold K. Type 1 diabetes as a relapsing- remitting disease? Nat Rev immunol 2007;7:988-94.

28. Elliott RB, Crossley JR, Berryman CC, James AG. Partial preservation of pancreatic beta-cell function in children with diabetes. Lancet 1981;2:1-4.
29. Silverstein J, Maclaren N, Riley W, Spillar R, Radjenovic D, Johnson S. Immunosuppression with azathioprine and prednisone in recent-onset insulin-dependent diabetes mellitus. N Engl J Med 1988;319:599-604.
30. Eisenbarth GS, Srikanta S, Jackson R, Rabinowe S, Dolinar R, Aoki T, *et al*. Anti-thymocyte globulin and prednisone Immuno therapy of recent onset type 1 diabetes mellitus. Diabetes Res 1985;2:271-6.
31. Skyler JS, Krischer JP, Wolfsdorf J, Cowie C, Palmer JP, Greenbaum C, *et al*. Effects of oral insulin in relatives of patients with type 1 diabetes: The Diabetes Prevention Trial-Type 1. Diabetes Care 2005;28:1068-76.
32. Thivolet CH, Goillot E, Bedossa P, Durand A, Bonnard M, Orgiazzi J. Insulin prevents adoptive cell transfer of diabetes in the autoimmune non-obese diabetic mouse. Diabetologia 1991;34:314-9.
33. Skyler JS. Update on worldwide efforts to prevent type 1 diabetes. Ann N Y Acad Sci 2008;1150:190-6.
34. Moore DJ, Kim JI, Sonawane S, Yeh H, Deng S, Lee K 4th, *et al.* Progress toward antibody-induced transplantation tolerance. Crit Rev Immunol 2007;27:167-218.
35. Herold KC, Hagopian W, Auger JA, Poumian-Ruiz E, Taylor L, Donaldson D, *et al*. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. N Engl J Med 2002;346:1692-8.
36. Hu CY, Rodriguez-Pinto D, Du W, Ahuja A, Henegariu O, Wong FS, *et al*. Treatment with CD20-specific antibody prevents and reverses autoimmune diabetes in mice. J Clin Invest 2007;117:3857-67.
37. Xiu Y, Wong CP, Bouaziz JD, Hamaguchi Y, Wang Y, Pop SM, *et al*. B lymphocyte depletion by CD20 monoclonal antibody prevents diabetes in nonobese diabetic mice despite isotype-specific differences in Fc gamma R effector functions. J Immunol 2008;180:2863-75.
38. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, Becker DJ, Gitelman SE, Goland R, *et al.* Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med 2009;361:2143- 52.
39. Larsen CM, Faulenbach M, Vaag A, Vølund A, Ehses JA, Seifert B, *et al*. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med 2007;356:1517-26.
40. Sherry NA, Chen W, Kushner JA, Glandt M, Tang Q, Tsai S, *et al.* Exendin-4 improves reversal of diabetes in NOD mice treated with anti-CD3 monoclonal antibody by enhancing recovery of beta-cells. Endocrinology 2007;148:5136-44.
41. Hong S. The natural killer T-cell ligand alpha-galactosylceramide prevents autoimmune diabetes in non-obese diabetic mice. Nat Med 2001;7:1052-6.
42. Herold KC, Gitelman SE, Masharani U, Hagopian W, Bisikirska B, Donaldson D, *et al*. A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. Diabetes 2005;54:1763-9.
43. Tisch R. Administering glutamic acid decarboxylase to NOD mice prevents diabetes. J Autoimmun 1994;7:845-50.
44. Tisch R. Induction of glutamic acid decarboxylase 65-specific Th2 cells and suppression of autoimmune diabetes at late stages of disease is epitope dependent. J Immunol 1999;163:1178-87.
45. Elliott JF, Qin HY, Bhatti S, Smith DK, Singh RK, Dillon T, *et al.* Immunization with the larger isoform of mouse glutamic acid decarboxylase (GAD67) prevents autoimmune diabetes in NOD mice. Diabetes 1994;43:1494-9.
46. Sai P, Rivereau AS, Granier C, Haertlé T, Martignat L. Immunization of non-obese diabetic (NOD) mice with glutamic acid decarboxylase-derived peptide 524-543 reduces cyclophosphamide-accelerated diabetes. Clin Exp Immunol 1996;105:330-7.
47. Li AF, Escher A. Intradermal or oral delivery of GAD encoding genetic vaccines suppresses type 1 diabetes. DNA Cell Biol 2003;22:227-32.
48. Menard V. Anti-GAD monoclonal antibody delays the onset of diabetes mellitus in NOD mice. Pharm Res 1999;16:1059-66.
49. Yoon JW. Control of autoimmune diabetes in NOD mice by GAD expression or suppression in beta cells. Science 1999;284:1183-7.
50. Jun HS. Prevention of autoimmune diabetes by Immuno-gene therapy using recombinant vaccinia virus expressing glutamic acid decarboxylase. Diabetologia 2002;45:668-76.
51. Raz1 I, Eldor R 2, Naparstek Y. Immune modulation for prevention of type 1 diabetes. Trends Biotechnol 2005;23:128-33.
52. Balasa B, Boehm BO, Fortnagel A, Karges W, Van Gunst K, Jung N, *et al*. Vaccination with glutamic acid decarboxylase plasmid DNA protects mice from spontaneous autoimmune diabetes and B7/ CD28 costimulation circumvents that protection. Clin Immunol 2001;99:241-52.
53. Bettini M, Castellaw AH, Lennon GP, Burton AR, Vignali DA. Prevention of autoimmune diabetes by ectopic pancreatic β-cell expression of interleukin-35. Diabetes 2012;61:1519-26.
54. Zhang J, Huang Z, Sun R, Tian Z, Wei H. IFN-g induced by IL-12 administration prevents diabetes by inhibiting pathogenic IL-17 production in NOD mice. J Autoimmun 2012;38:20-8.
55. Mandke R, Singh J. Cationic nanomicelles for delivery of plasmids encoding interleukin-4 and interleukin-10 for prevention of auto-immune diabetes in mice. Pharm Res 2012;29:883-97.
56. Ann NY. Interleukin-10 plasmid construction and delivery for the prevention of type 1 diabetes. Ann N Y Acad Sci 2006;1079:313-9.
57. Nicoletti F, Trepicchio WL, Lgssiar HG, Hassan M. Interleukin-11 Inhibits NF-κB and AP-1 Activation in Islets and Prevents Diabetes Induced with Streptozotocin in Mice. Exp Biol Med (Maywood) 2004;229:425-436.
58. Masteller EL, Warner MR, Ferlin W, Judkowski V, Wilson D, Glaichenhaus N, *et al.* Peptide-MHC class II dimers as therapeutics to modulate antigen-specific T cell responses in autoimmune diabetes. J Immunol 2003;171:5587-95.
59. Elias D, Markovits D, Reshef T, van der Zee R, Cohen IR. Induction and therapy of autoimmune diabetes in the non-obese diabetic (NOD/LT) mouse by a 65-kDa heat shock protein. Proc Natl Acad Sci U S A 1990;87:1576-80.
60. Elias D, Cohen IR. The hsp60 peptide p277 arrests the autoimmune diabetes induced by the toxin streptozotocin. Diabetes 1996;45:1168- 72.
61. Elias D. Induction of diabetes in standard mice by immunization with the p277 peptide of a 60-kD a heat shock protein. Eur J Immunol 1995;25:2851-7.
62. Raz I, Elias D, Avron A, Tamir M, Metzger M, Cohen IR. Beta-cell function in new-onset type 1 diabetes and immuno-modulation with a heat-shock protein peptide: A randomized, double-blind, phase II trial. Lancet 2001;358:1749-53.
63. Phillips B, Trucco M, Giannoukakis N. Current state of type 1 diabetes immunotherapy: Incremental advances, huge leaps, or more of the same? Clin Dev Immunol 2011;2011:432016.
64. Ludvigsson J. The role of immunomodulation therapy in autoimmune diabetes. J Diabetes Sci Technol 2009;3:320-30.

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